

Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants

Ludvigsson JF, Mostrom M, Ludvigsson J, Duchén K. Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. *Pediatr Allergy Immunol* 2005; 16:201–208. ©2005 Blackwell Munksgaard

Earlier studies on breastfeeding and atopy in infants have yielded contradictory results. We examined the relationship between exclusive breastfeeding and atopic dermatitis (AD) in a cohort of infants born between 1 October 1997 and 1 October 1999 in south-east Sweden. We evaluated the risk of AD 'at least once' or 'at least three times' during the first year of life in relation to duration of exclusive breastfeeding: <4 months (short exclusive breastfeeding; SEBF) vs. ≥4 months. All data were obtained through questionnaires. Of 8346 infants with breastfeeding data, 1943 (23.3%) had suffered from AD during the first year of life. Duration of exclusive breastfeeding was not associated with lower risk of AD ($p = 0.868$). SEBF did not influence the risk of any AD (OR = 1.03; 95% CI OR = 0.91–1.17; $p = 0.614$) or AD at least three times (OR = 0.97; 95% CI OR = 0.81–1.16; $p = 0.755$) during the first year of life. Adjustment for confounders did not change these point estimates. Neither was there any link between SEBF and risk of AD among infants with a family history of atopy [adjusted odds ratio (AOR) = 1.16; 95% CI AOR = 0.90–1.48; $p = 0.254$]. Furred pets at home were linked to a lower risk of AD both among infants with a family history of atopy (AOR = 0.76; 95% CI AOR = 0.60–0.96; $p = 0.021$) and among infants with no such history (AOR = 0.79; 95% CI AOR = 0.69–0.90; $p < 0.001$). Infants with no family history of atopy were less prone to develop AD if parents smoked (AOR = 0.76; 95% CI AOR = 0.61–0.95; $p = 0.016$). This study indicates that exclusive breastfeeding does not influence the risk of AD during the first year of life, while presence of furred pets at home seems to be negatively associated with AD.

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Key words: atopy; breastfeeding; child; eczema; atopic dermatitis; smoking

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Accepted 23 December 2004

The relationship between breastfeeding and the development of atopic manifestations early in life, i.e. atopic dermatitis (AD) and food allergy, has been controversial for the last 50 yr (1). While some studies have supported an inverse relationship (2–9), others have failed to show any such relationship (10–15). In some of the studies yielding positive results (2–7), the authors have not considered the confounding effect of other environmental factors such as smoking (10–13). Many studies, reporting no relationship between breastfeeding and atopy, lack defined diagnostic criteria and adjustment for potential environmental confounders. In two

positive studies, data on diagnostic criteria are insufficient (4, 5).

Late solid food introduction in breast-fed babies is linked to a lower prevalence of atopic symptoms during the first years of life (4–6) and after 10 yr of follow-up (16). Mothers of atopic infants also tend to breastfeed for a longer time and introduce solid foods later than control mothers (17).

In Sweden, breastfeeding has been linked to a lower risk of atopic disease in children with a family history of atopy (18) and also in the general child population (19). Meanwhile, the prevalence of allergic diseases and that of

breastfeeding has increased worldwide (20, 21). This would argue against any link between a 'short' duration of exclusive breastfeeding and atopy.

The major determinant for allergy development is genetic susceptibility. If one of the parents is allergic, the offspring's risk for allergy doubles (22), if both parents are affected, the risk increases four to six times, sometimes more (23). Non-nutritional environmental factors may also be of importance to the risk of AD. Smoking exerts a negative influence on breastfeeding pattern (24) and is linked to an increased risk of AD (25). With few exceptions (26), previous studies on allergy and breastfeeding have not validated smoking data against Cotinine measurements (the major breakdown product of nicotine). Late introduction of solid foods as well as furred pets at home have both been linked to a lower risk of AD (27). Other risk factors for allergic disease include preterm birth (28), maternal level of education and presence of older siblings (29).

The main objective of this study was to assess the relationship between exclusive breastfeeding duration, especially 'short exclusive breastfeeding' (SEBF, exclusive breastfeeding < 4 months), and risk of AD in the first year of life adjusting for potential confounders. A second objective was to study a number of other suspected risk factors and AD.

Materials and methods

The parents to all babies born in south-east Sweden between 1 October 1997 and 1 October 1999 ($n = 21700$) were invited to participate in a project to study the importance of environmental factors for the development of autoimmune and allergic diseases [the All Babies In Southeast Sweden (ABIS) study] (Fig. 1). The parents of 17,055 infants (78.6%) gave their informed consent to participate. Shortly after birth, at the maternity ward, the mothers received a questionnaire including questions about socio-economic background and heredity for allergic disease (completed by 16,286 mothers).

The mother completed the birth questionnaire just before leaving the maternity ward or at home (and in the latter case returned to the responsible nurse/doctor at the time of regular infant check-up). Of 16,286 study participants, 10,836 completed the 1-yr questionnaire. In this group, 94.2% responded to the question: 'For how many months did the child receive only breast milk?' and 81.1% to the question: 'Has the child suffered from itching eczema during his/her first year of life?' With regard to the presence of

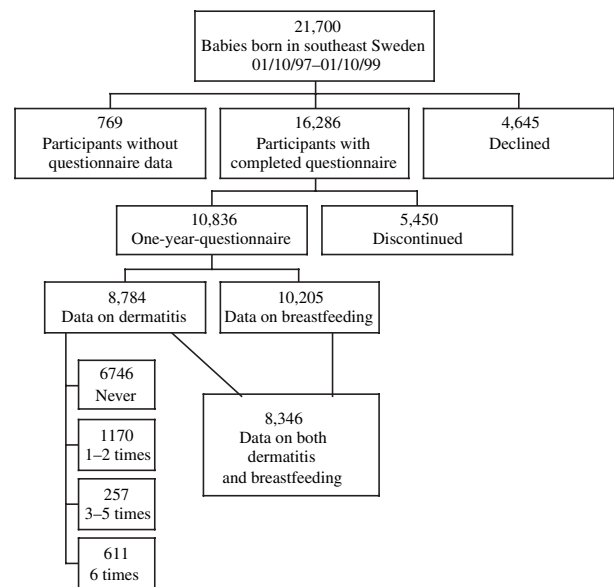


Fig. 1. Flow chart of study participants.

itching eczema, mothers were offered the four alternatives: 'never', 1–2 episodes, 3–5 episodes and ≥ 6 episodes (Fig. 1). 'Any AD' was defined as ≥ 1 itching eczema episode; severe AD was defined as ≥ 3 episodes of itching eczema. If not specifically indicated to be otherwise, 'AD' and 'cases' in this paper refer to 'any AD'. Data on both exclusive breastfeeding duration and AD were available in 8346 infants. Controls consisted of infants who had never suffered from AD. The calculations of 'severe AD' vs. controls were based on 6954 infants.

Mothers were offered nine alternatives (monthly intervals) with regard to exclusive breastfeeding duration, 'more than 8 months' was the last alternative. Children with an exclusive breastfeeding duration > 8 months were given a censored value of 8 months when included in the survival analyses.

In order to validate the breastfeeding data, mothers were also asked if and at what age the infant had first been fed breast milk substitute/formula/gruel and foods containing gluten (bread, pasta and foods containing flour). These are foods commonly introduced to Swedish infants after exclusive breastfeeding. In no questionnaire, were there any discrepancies between reported exclusive breastfeeding duration and age at introduction of complementary foods, hence no infant was excluded for reasons of contradicting infant feeding data.

At the time of data collection, the WHO recommended 4–6 months of exclusive breastfeeding. For that reason we chose to define SEBF as < 4 months.

Covariates

The following covariates were included in our model of exclusive breastfeeding duration vs. risk of AD in order to adjust for potential confounding: smoking, furred pets, preterm birth, maternal education, parity and atopic heredity. Exposure to furred pets was defined as presence of cat, dog or guinea-pig at the infant's home. Preterm birth was defined as gestational age < 37 completed weeks. At birth, mothers were asked about smoking during pregnancy and at 1 yr after birth they were asked for any smoking at home during the child's first year of life. Infants whose mother had indicated parental smoking at either of these moments were regarded as exposed to smoking. We also asked for parity as well as history of asthma, cow milk protein allergy or allergy to other kind of food in mother, father or sibling (family history of atopy). All categories were pre-defined. Maternal education was dichotomized (non-university education vs. university education).

As children in Sweden are not allowed to attend day care outside home until after the age of 1 yr, we did not include day care among the covariates.

Statistical methods

Main analyses

We used Cox's proportional hazards method to determine hazard ratios (HR) for exclusive breastfeeding duration. $HR > 1$ indicates an increased risk of shorter exclusive breastfeeding. The number of censored values was < 4% of the total number of respondents in all survival analyses. Pearson chi-square test (with Yates' correction) was used to compare proportions.

Binary logistic regression was used to calculate odds ratios. 95% confidence intervals (CI) for the adjusted odds ratios (OR) not including 1.00 were considered statistically significant.

Subgroup analyses

We stratified for family history of atopy (Table 2). Furthermore, cases were compared with controls excluding infant controls with reported cow milk protein intolerance (but no AD). This was done in order to reduce the number of false-negative infants.

Population attributable fraction

We calculated the population attributable fraction for SEBF and risk of any AD. The population

attributable fraction for cases (vs. controls) was estimated as follows: prevalence of the studied exposure among the cases $\times$ $AOR - 1 / AOR$. Statistics was calculated using the statistical software SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

Statistical power

Setting alpha (α) to 0.05, we had an 80% power ($1 - \beta$) to detect statistically significant differences in the proportion of infants being exclusively breastfed for < 4 months between controls (1366/6403 infants were SEBF; 21.3%) and infants with AD, if at least 470/1943 (24%) of infants with AD had been exclusively breastfed for < 4 months. We used Sample Power 2.0 to calculate the statistical power (30).

Ethics

This study was part of the ABIS study, which has been approved by the Research Ethics Committees of the Faculty of Health Sciences, Linköping University and the Medical Faculty of Lund University. Mothers gave their consent after careful written as well as verbal information and information via videotape.

Results

Background data

Of 8784 infants with data on AD in the questionnaire, 2038 (23.2%) had suffered from AD at least once during the first year of life (Fig. 1). Among controls, 122 had indicated cow milk protein intolerance but no concomitant AD during the first year of life. Among infants with data on AD there were data on exclusive breastfeeding in 95% [$n = 8346$; 1791 were exclusively breastfed for < 4 months (SEBF)]. One in five infants had a family member with asthma, cow milk allergy or other food allergy (1942/8784, 22%) and one in nine lived in a household where either of the parents smoked (993/8784, 11%). One-third of the respondents had a dog, a cat or a guinea-pig at home (3149/8784, 36%).

Exclusive breastfeeding and risk of AD

Duration of exclusive breastfeeding did not differ between controls and infants with AD (1–2 episodes during the first year of life: $HR = 1.03$, 95% CI = 0.97–1.10, $p = 0.334$; 3–5 episodes: $HR = 0.91$, 95% CI = 0.80–1.03,

$p = 0.144$; ≥ 6 episodes: HR = 1.00; 95% CI = 0.92–1.09, $p = 0.948$ (censored = 305/8346). Children with any AD (HR = 1.00; 95% CI = 0.95–1.06, $p = 0.868$) or severe AD (HR = 0.97; 0.90–1.04; $p = 0.336$) did not differ from controls with regards to exclusive breastfeeding duration. When adjusting for potential confounders, hazard ratios remained around 1 (any AD: HR = 1.01; severe AD: HR = 0.96).

Of 1943 infants with AD, 425 had been exclusively breastfed for <4 months when compared with 1366/6403 controls (risk of any AD if infant had been exclusively breastfed <4 months: OR = 1.03; 95% CI = 0.91–1.17; $p = 0.614$). Excluding infants with cow milk protein intolerance from controls did not affect the point estimate (data not shown).

Less than 4 months of exclusive breastfeeding (SEBF <4 months) was not linked to an increased risk of severe AD (OR = 0.97; 95% CI = 0.81–1.16; $p = 0.755$).

Adjusting for potential confounders, there was still no association between SEBF and risk for any AD or severe AD (Table 1). The population attributable fraction for cases was 0.014. Assuming a causal relationship between SEBF and any AD, this would mean that if all infants were exclusively breastfed at least 4 months (now 21.9% of cases were not) we would reduce the number of infants with any AD by some 1.4%.

Pets and smoking

Presence of furred pets at home was linked to a lower risk of both any and severe AD (Table 1). Parental smoking was linked to a lower risk of any AD (particularly in children with no family history of atopy as seen in Tables 1 and 2) but not to severe AD (Table 1). Excluding infants with a cow milk protein intolerance from controls did not affect the point estimates (data not shown).

Table 1. Exclusive breastfeeding duration and risk of atopic dermatitis

	Any atopic dermatitis*			Severe atopic dermatitis*		
	AOR	95% CI AOR	p-value	AOR	95% CI AOR	p-value
Exclusive breastfeeding <4 months	1.07	0.94–1.21	0.310	0.98	0.81–1.18	0.834
Parental smoking	0.81	0.67–0.97	0.019	0.86	0.67–1.11	0.259
Gestational age <37 wk	0.82	0.62–1.10	0.190	0.89	0.59–1.33	0.575
Maternal education: university	1.08	0.96–1.20	0.193	1.02	0.87–1.19	0.812
Older sibling	0.94	0.85–1.05	0.281	0.85	0.73–0.99	0.031
Furred pets	0.75	0.67–0.84	<0.001	0.61	0.52–0.72	<0.001
Constant	0.34		0	0.14		0

The adjusted odds ratio for any atopic dermatitis in preterm children was 0.82, with a 95% confidence interval for the adjusted odds ratio of 0.62–1.10, hence preterm birth is not a risk factor for any atopic dermatitis in this study ($p = 0.190$). AOR, adjusted odds ratio; 95% CI AOR = 95% confidence interval for the adjusted odds ratio.

*We asked the mother: ‘Has the child suffered from eczema/AD during his/her first year of life?’ Mothers were offered the alternatives ‘never’, one to two times, three to five times and six times or more. Any atopic dermatitis indicates children with ≥ 1 episode of atopic dermatitis; severe dermatitis indicates children with ≥ 3 episodes. Controls consist of infant who had never suffered from eczema/AD.

Table 2. Exclusive breastfeeding duration and risk of at least one episode of atopic dermatitis

	Atopy in family*			No atopy in family*		
	AOR	95% CI AOR	p-value	AOR	95% CI AOR	p-value
Exclusive breastfeeding <4 months	1.16	0.90–1.48	0.254	1.04	0.90–1.21	0.595
Parental smoking	0.86	0.62–1.19	0.352	0.76	0.61–0.95	0.016
Gestational age <37 wk	0.87	0.52–1.47	0.611	0.78	0.54–1.11	0.160
Maternal education: university	1.19	0.96–1.47	0.115	1.03	0.91–1.18	0.638
Older sibling	0.99	0.81–1.22	0.950	0.91	0.80–1.03	0.127
Furred pets	0.76	0.60–0.96	0.021	0.79	0.69–0.90	<0.001
Constant	0.44		0	0.31		0

Calculations based on 1817 (family history of atopy) and 6202 infants (no family history of atopy). The adjusted odds ratio for any atopic dermatitis in preterm children with a family history of atopic disease (left column) was 0.87, with a 95% confidence interval for the adjusted odds ratio of 0.52–1.47, hence in this study, preterm birth is not a risk factor for any atopic dermatitis among children with a family history of atopy ($p = 0.611$). AOR, adjusted odds ratio; 95% CI AOR = 95% confidence interval for the adjusted odds ratio.

*Familial atopy was defined as history of asthma, cow milk protein allergy or allergy to other kind of food in mother, father or sibling. See footnote to Table 1 for an explanation of atopic dermatitis.

Infants with heredity for atopy

Duration of exclusive breastfeeding did not differ between cases with any AD (HR = 1.02; 95% CI = 0.92–1.13; $p = 0.665$) or severe AD (HR = 1.00; 95% CI = 0.88–1.14, $p = 0.947$) and controls (censored = 83/1767). SEBF was not associated with increased risk of any AD (OR = 1.16; 95% CI = 0.90–1.48; $p = 0.254$), neither was exclusive breastfeeding duration using cut-offs at either 2 or 6 months associated with increasing risk of any AD (data not shown). Adjusting for potential confounders we found no association between SEBF and risk of any AD (Table 2). Presence of furred pets at home was linked to a lower risk of any AD both among infants with a family history of atopy and in those lacking such history (Table 2).

Infants with no heredity for atopy

Duration of exclusive breastfeeding did not differ between cases with any AD (HR = 1.01; 95% CI = 0.95–1.07; $p = 0.794$) or severe AD (HR = 0.96; 95% CI = 0.88–1.05, $p = 0.370$) and controls (censored = 222/6496). SEBF was not associated with increased risk of any AD (OR = 1.04; 95% CI = 0.90–1.21; $p = 0.595$) (Table 2), neither was exclusive breastfeeding duration using cut-offs at either 2 or 6 months associated with risk of any AD (data not shown).

Adjusting for potential confounders we found no association between SEBF and risk of AD (Table 2). In infants with no family history of atopy, parental smoking was associated with a lower risk of AD (Table 2). This was not the case in infants with a family history of atopy.

Discussion

We found no evidence that exclusive breastfeeding influences the development of AD in 1-yr-old children. This finding contrasts to that of both older (3–6) and more recent studies (19, 31, 32), although research in this area is in no way consistent, e.g. Bergmann et al. reported a positive relationship between breastfeeding and AD in early life (33).

Different study designs (32), including the type of breastfeeding being studied (33, 34) and the use of skin prick test in the definition of AD (3), may partly explain the divergent results. In our study, we rely on maternal reports of AD.

In a study from Belarus (31), breastfeeding was linked to a 46% risk reduction of AD in the first 12 months of life. In that study, the participants

consisted of children whose mothers were either assigned to breastfeeding support or not. Differences in data collection methods may explain the different results between the current study and that reported by Kramer et al. (31).

Optimally, the relationship between environmental factors and AD should be evaluated through a prospective study of unselected newborns where there is a prospective proper monitoring of well defined environmental factors like breastfeeding, a proper monitoring of AD based on clear diagnostic criteria confirmed by examination of the children and interviews of the parents.

In a recent Swedish study (19), sharing many of the characteristics of the present study, Kull et al. reported a very small decrease in AD in the first 2 yr among children exclusively breastfed for more than 4 months compared to <4 months (27% vs. 25%). Even if Kull et al. (19) demanded several criteria to be fulfilled for a diagnosis of AD and we based our study on maternal report of AD (and rather focused on frequency of AD), the results were similar in that we found little influence of breastfeeding.

We found that furred pet keeping is associated with a lower risk of AD in infants, irrespective of previous atopy in other family members. This is in line with the study by Schoetzau et al. (27). The mucosal immune system of the newborn infant can be triggered to produce specific antibodies against bacteria colonizing the intestine (35). This may influence the immune response to other antigens, like furred pet allergen and food allergen. Early exposure to furred animals with high allergenic load could also exert a protective effect. Several studies have suggested that the fetus initiates immune responses to the major cat allergen already before birth (36, 37). Furthermore, high levels of cord blood immunoglobulin G (IgG) antibodies to cat allergen seem to be associated with fewer atopic symptoms during the first 8 yr of life (37). We do not think that the inverse relationship between furred pet exposure and AD are due to an avoidance of furred pets in families with atopic heredity. Atopic families may well avoid pets although pet keeping in our study was related to a lower risk for AD in the first year of life independently of atopic heredity. Still, we cannot exclude that misclassification of moderate atopic heredity has biased our estimates.

Parental smoking was associated with a lower risk of AD; this was explained by a lower risk estimate in the stratum with infants who lacked family history for atopic disease. It could be that our definition of atopic heredity (only including

children whose mother, father or sibling suffered from asthma, cow milk protein allergy or allergy to other kind of food) was narrower than in other studies, creating a false-negative familial history of AD and thus influencing our results. In children with a heredity of atopy but misclassified as lacking heredity of atopy, we can assume a higher risk of AD due to genetic factors and low degree of smoking due to the presence of other family members with atopy. That would lead to a negative correlation between parental smoking (occurring more commonly in families that were truly non-atopic) and AD (occurring more often in families that were truly atopic but in this study classified as non-atopic) among subjects that were in this study classified as having no atopic heredity.

However, we cannot exclude that other factors not evaluated in this study interact with smoking and under certain circumstances decrease the risk of AD.

Strengths and limitations

This study is part of a population-based cohort study. In a sample of infants in this study, questionnaire data on smoking were validated through measurements of urine Cotinine in the study population (38). The lack of differentiation between maternal and paternal smoking in our study is a weakness. It may well be that in very young infants maternal smoking confers a greater exposure to smoking than does paternal smoking.

Previous research in the study area has shown a high correlation between questionnaire data on breastfeeding and data on breastfeeding reported independently of any study at child health care centres (39). Even if mothers are often well aware of the duration of exclusive breastfeeding in their latest child (40), we cannot exclude recall bias as breastfeeding data were collected at 1 yr of age (41). As we did not ask for intake of syrups, medicines and smaller amounts of liquid, this study deviates from the strict definition of exclusive breastfeeding suggested by Labbok and Krasovec (34). However, the purpose of the current study was not to establish the distribution of exclusive breastfeeding duration in the general population but to study the relationship between exclusive breastfeeding and risk of AD. For that purpose we deem our methodology accurate enough.

Regarding AD, we asked mothers to report the presence of AD. This means that the severity of disease varies and there is a risk that 'low intensity AD' is not of atopic nature. Still, the

prevalence of AD in our study (23.2%) is well in line with that of previous studies (4, 19, 42). We cannot exclude a certain degree of misclassification, which may have blurred our results. In order to minimize such blurring we also compared cases with controls excluding controls with cow milk protein allergy (a sign of atopy); we also compared controls with infants with severe AD.

Another drawback of the current study is the low response rate of the 1-yr questionnaire (about 67%). The 1-yr questionnaire was not followed by any questionnaire/postcard/telephone follow-ups. Considering that, the response rate is not lower than in studies with similar design (43). Besides, the number of participants was large enough to detect even small differences.

A low response rate could be associated with selection bias. But that would only alter the point estimates if the proportion of, for example, 'dropout' mothers who breastfed exclusively for <4 months and had a child affected by AD was different from the proportion of 'participating' mothers who breastfed exclusively for <4 months and had a child affected by AD. We find this type of selection bias unlikely, although it cannot be excluded.

In conclusion, we found no link between exclusive breastfeeding pattern and atopic AD in the first year of life, even if there was a family history of atopy. Meanwhile, the presence of furred pets at home was associated with a lower risk of AD in the first year of life.

Acknowledgments

We are grateful to all the children and parents who participated in ABIS, and to all staff members at participating Mother and Baby Health Care Centres and obstetric departments, whose willingness to collaborate has been of crucial importance. Many thanks to ABIS nurses Caroline Berggren, Christina Larsson and Iris Franzén, who have been so enthusiastic and encouraging.

Supported by the JDF-Wallenberg Foundation (K98-99JD-12813-01A, No. 1997-73), the Swedish Medical Research Council (MFR) K99-72X-11242-05A, the Swedish Child Diabetes Foundation (Barndiabetesfonden), Söderbergs Foundation, the Novo Nordisk Foundation, the Sven Jerring Foundation, Örebro University Hospital, Clinical Epidemiology Unit at the Karolinska University Hospital, and FORSS (2000-323).

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